Oct4 Cell-Autonomously Promotes Primitive Endoderm Development in the Mouse Blastocyst.

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Authors: Tristan Frum, Michael A Halbisen, Chaoyang Wang, Hossein Amiri, Paul Robson, Amy Ralston

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Public Summary:
In this study, we focus on understanding the transcription factor Oct4, an essential node in the network of transcription factors that establishes and maintains pluripotency. Oct4 has been well studied in pluripotent stem cells in vitro, however, less is known about the roles of Oct4 during the earliest phases of development during which Oct4 is expressed in both pluripotent and non-pluripotent cell types. Here, by investigating the role of Oct4 during early development, we show that while Oct4 is essential for bona fide pluripotency, some aspects of the pluripotency network, such as the expression of other master regulators of pluripotency, are Oct4-independent. Surprisingly, we find that Oct4 is essential for the development of a non-pluripotent cell type, demonstrating that Oct4 performs essential roles in differentiation independent of Oct4's role in maintaining pluripotency in stem cells. Finally, we show that Oct4 is required for normal metabolism in the developing embryo. Taken together, this study identifies multiple roles for the pluripotency factor Oct4 in the early embryo and broadens our understanding of Oct4 as a transcription factor regulating multiple developmental processes including the establishment and maintenance of pluripotency as well as the opposing activity of promoting differentiation. Understanding how these multiple activities of Oct4 are regulated will greatly enhance the safety and efficacy of pluripotent stem cells in regenerative medicine.

Scientific Abstract:
In embryonic stem (ES) cells and in early mouse embryos, the transcription factor Oct4 is an essential regulator of pluripotency. Oct4 transcriptional targets have been described in ES cell lines; however, the molecular mechanisms by which Oct4 regulates establishment of pluripotency in the epiblast (EPI) have not been fully elucidated. Here, we show that neither maternal nor zygotic Oct4 is required for the formation of EPI cells in the blastocyst. Rather, Oct4 is first required for development of the primitive endoderm (PE), an extraembryonic lineage. EPI cells promote PE fate in neighboring cells by secreting Fgf4, and Oct4 is required for expression of Fgf4, but we show that Oct4 promotes PE development cell-autonomously, downstream of Fgf4 and Mapk. Finally, we show that Oct4 is required for the expression of multiple EPI and PE genes as well as multiple metabolic pathways essential for the continued growth of the preimplantation embryo.